REMARKS

I. Information Disclosure Statement

The Examiner has not yet returned an initialed copy of the PTO Form 1449 which accompanied the Information Disclosure Statement filed on June 10, 2004. Applicants have included a copy of the PTO Form 1449 (which accompanied the IDS filed June 10, 2004), and again respectfully request the Examiner to initial it thereby indicating that all references have been considered.

II. Amendments to the Claims

Claims 13-17 are all the claims pending in the application.

Claim 13 has been amended to define HGF ("hepatocyte growth factor"), VEGF ("vascular endothelial growth factor"), and HVJ ("hemagglutinating virus of Japan") the first time these abbreviations are used in the claims.

Claim 14 has been amended to clarify that the claimed method is intended to treat or prevent reduced blood flow.

Claims 13-17 have been amended to recite "a polynucleotide encoding" rather than a "gene." This amendment is supported at pages 16-18 and 32 of the specification.

All of the amendments outlined above are purely editorial in nature and are not intended to change the scope of the claims.

III. Claim Objections

At page 2 of the Office Action, claim 13 was objected to because the abbreviations "HGF," "VEGF," and "HJV" should be spelled out the first time they appear in the claims.

As noted above, Applicants have amended claim 13 as required by the Examiner.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection.

IV. Claim Rejections Under 35 USC § 112 -Indefiniteness

At pages 2 and 3 of the Office Action, claims 13-17 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 13-17

Specifically, the Examiner contended that claims 13-17 are vague and indefinite because the meaning of the term "gene" is not clear in the context of the claims.

Applicants have deleted the term "gene" and have further amended the claims to recite "a polynucleotide encoding HGF and/or a polynucleotide encoding VEGF." Applicants assert that the claims as amended particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Thus, Applicants respectfully request reconsideration and withdrawal of this aspect of the rejection.

B. Claim 14

The Examiner also contended that claim 14 is vague and indefinite because the preamble is inconsistent. The Examiner explains that the preamble recites a "method for reduced blood flow," whereas the specification teaches increasing blood flow and the method step recites treating or preventing reduced blood flow.

Applicants have amended the preamble of claim 14 to recite methods "for treating or preventing reduced blood flow."

Accordingly, Applicants respectfully request reconsideration and withdrawal of this aspect of the rejection.

V. Claim Rejections Under 35 USC § 103(a) - Obviousness

At page 3 of the Office Action, claims 13-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Isner et al. (US 6,121,246 or WO 97/14307) and Morishita et al. (US 6,248,722), in view of Ghodsi et al. (Hum Gene Ther 1998; 9:2331-40), Yonemitsu et al. (Gene Ther 1997;4:631-8), and Wang et al. (Biochem Biophy Comm 1998;244:449-54), and as evidenced by Rosengart et al. (Circulation 1999;100:468-74) and Furlan et al. (Hum Gene Ther 1998;9:2605-17).

The Examiner maintained her position that the present invention is obvious because Isner and Morishita teach treating ischemia with HGF and VEGF via HVJ-liposomes in multiple cell types and tissues, while Ghodsi teaches delivery of a therapeutic gene to the brain.

Briefly, the Examiner contended that HGF and VEGF are known to promote therapeutic angiogenesis in many different organs and tissues, and nothing on record indicates that such an

effect would not be expected in brain tissue. Furthermore, the Examiner contended that significant levels of transgene expression in brain tissue and subsequent biological effects have been observed for different types of therapeutic proteins such as human tissue kallikrein gene (Wang), β-glucuronidase (Ghodsi), and Interleukin-4 (Furlan), and nothing on record indicates that such expression and effect would not occur for VEGF or HGF in the brain. The Examiner appeared to base the assertions of the expectation of a person of ordinary skill in the art on an assumption that cardiac and skeletal muscle are representative of brain tissue, and that human tissue kallikrein, β-glucuronidase, and Interleukin-4 are representative of VEGF and HGF.

The Examiner acknowledged that Ghodsi describes delivery via an adenoviral vector rather than HVJ-liposomes, but contended that Yonemitsu teaches the advantages of HVJ-liposomes, thereby providing motivation to use HVJ-liposomes as well as a reasonable expectation of success. In particular, the Examiner stated that although Yonemitsu describes delivery to airway epithelium, not brain tissue, the HVJ-liposome effect does not appear to be tissue specific because Morishita has shown that the liposomes function in vascular endothelial cells, muscle cells, and articular cells. Thus, according to the Examiner, the success of HGF and VEGF gene therapy via HVJ-liposomes would be reasonably expected in the brain.

Applicants respectfully traverse the rejection, for at least the following reasons.

As detailed in the previous response filed April 6, 2004, and in the Declaration filed May 11, 2004, Applicants maintain that a person of ordinary skill in the art would not have predicted with a reasonable expectation of success that polypeptides encoding HGF and/or VEGF

administered in the form of HVJ-liposomes into the subarachnoid space would be effective for treatment of cerebrovascular disorders.

First, as previously argued, none of the cited references teaches gene therapy using HGF or VEGF expression in the brain. In addition, none of the cited references teaches gene therapy via HVJ-liposome-mediated delivery to the brain. Thus, given the unpredictability of gene therapy, particularly in the brain, the references do not provide a reasonable expectation of success for the methods of the present invention, which methods combine the two novel conditions outlined above. Applicants assert that the new references cited by the Examiner in the outstanding Office Action, namely Yonemitsu, Wang, Rosengart, and Furlan, do not support the Examiner's position.

Specifically, similar to Ghodsi, neither Wang nor Furlan disclose delivery to and expression of HGF or VEGF HJV-liposomes in the brain, instead describing delivery and expression of a different gene via a different vector. Furthermore, Yonemitsu does not demonstrate the use of HVJ-liposomes in the brain. Finally, Rosengart, like Morishita, only describes the administration of VEGF genes to cardiac muscle, not to the brain.

As noted above, the Examiner appears to be assuming that human tissue kallikrein, β-glucuronidase, and Interleukin-4 are representative of VEGF and HGF. However, there is no reasonable relationship between human tissue kallikrein, β-glucuronidase, and Interleukin-4 on the one hand, and VEGF and HGF on the other. Kallikrein and β-glucuronidase are enzymes, and are quite different from VEGF and HGF both structurally and with regard to biological activity. Specifically, kallikrein is involved in blood pressure control and β-glucuronidase is a

metabolic enzyme, while both VEGF and HGF are growth factors. In addition, although interleukin-4 is a cytokine, this protein promotes T.B. cell propagation and differentiation, mast cell propagation, resting phase B cell activation, IgG1 and IgE production, receptor propagation, and the like. In contrast, VEGF and HGF act on vascular cells. Finally, human tissue kallikrein, β-glucuronidase, and Interleukin-4 were all expressed using viral vectors, not the HVJ-liposomes of the present invention. Thus, based on the cited references, a person of ordinary skill in the art would not have reasonably expected VEGF and HGF to be effectively expressed in the brain.

Furthermore, the Examiner contended that Yonemitsu and Morishita disclose that HVJ-liposome-mediated delivery is not tissue-specific. However, Yonemitsu discloses only gene delivery to the lung, and does not teach or suggest delivery to the brain. In addition, this reference teaches away from HVJ-liposomes and describes the use of a different gene transfer system, HVJ-cationic liposomes, for in vivo gene transfer to lung airway epithelium, stating that HVJ-liposomes were ineffective for this purpose. Yonemitsu also points to other problems with the HVJ-liposome vector system (see page 631). Furthermore, Morishita discloses use of HVJ-liposomes for administration to muscle, but teaches nothing of delivery to the brain. The Examiner has not shown that delivery to muscle and delivery to brain are equivalent for purposes of gene therapy. Therefore, a person of ordinary skill in the art would not have reasonably expected HVJ-liposomes to be successful in the present invention.

Applicants have previously argued that gene therapy, particularly in the brain, remains a highly unpredictable art. As further evidence regarding the unpredictability of gene therapy in the brain, Applicants submit herewith copies of two additional articles, Rainov and Ren, *Gene*

Therapy for Human Malignant Brain Tumors, Cancer J. (2003), vol. 9, no. 3, pp. 180-188, and Tenenbaum et al., *Neuroprotective Gene Therapy for Parkinson's Disease*, Current Gene Ther. (2002), vol. 2, no. 4, pp. 451-483.

Rainov and Ren describe multiple obstacles to the transfer of therapeutic genes to tumor cells within the brain. In particular, the authors state that "the failure of most clinical gene therapy protocols to produce significant and unequivocal benefit to brain tumor patients seems to be mainly due to the low tumor cell transduction rate observed in vivo, but it may also depend on the respective physical delivery strategy of the vector." Rainov, p. 180. The authors also note at page 185 that liposomes have not generally been used in clinical trials in brain tumors, "mainly for reasons of efficacy of gene transfer and because of transgene delivery issues." The authors conclude that "gene therapy is a highly complex paradigm for the treatment of brain tumors." Rainov, p. 186.

Tenenbaum et al. explain that "in non-dividing cells, in particular [those] of the nervous system, transport of DNA to the nucleus is a major limiting state for non-viral DNA delivery. Therefore, *gene transfer using liposomes has generally failed in the brain*." Tenenbaum, p. 465 (emphasis added). The authors report that "several aspects of gene transfer, such as uncontrolled diffusion, axonal transport, unpredictable site of integration and immunological responses, still raise safety concerns and justify further development of viral and non-viral vectors as well as genetic elements with tightly controlled gene expression." Tenenbaum, abstract, p. 451.

Applicants also point out that the PTO itself recognized the unpredictability of gene therapy, and the particular challenges associated with gene delivery to the brain, in the enablement rejection issued August 28, 2002 in the present application.

Applicants submit that the teachings of the references cited by the Examiner do not teach or suggest gene therapy to the brain using HGF and/or VEGF. In addition, the references do not teach or suggest using HVJ-liposomes in the brain. The Examiner may possibly have demonstrated that it would be "obvious to try" gene therapy using HGF and/or VEGF administered in the form of HVJ-liposomes into the subarachnoid space for the treatment of cerebral occlusive diseases. However, given the unpredictability of gene therapy, especially in the brain, the teachings of the cited references clearly do not provide a reasonable expectation of success.

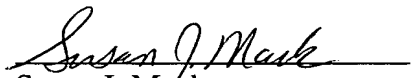
Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

VI. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	09/856,374
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First Named Inventor	Ryuichi MORISHITA
Art Unit	1632
Examiner Name	Qian Janice LI
Attorney Docket Number	Q64360

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US			
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Foreign Patent Document: Number[4]	Foreign Patent Document: Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		Chinese Office Action for Chinese Patent Application No. 00802004.3 dated February 4, 2004	Yes

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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